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10/612,356	07/02/2003	Ralph Zahn	26563U	5402

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EXAMINER	
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ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,356	ZAHN ET AL.	
	Examiner	Art Unit	
	LARRY D. RIGGS II	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *10-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed 03 July 2008 are acknowledged and entered.

Status of Claims

Claims 1-29 are currently pending. Claims 10-29 are withdrawn. Claims 1-9 are considered on the merits.

Withdrawn Rejections/Objections

The objection to claims 4-6, in the Office action mailed 03 January 2008 is withdrawn in view of the amendments filed 03 July 2008.

The rejection of claims 1-9 under 35 U.S.C. 112, Second Paragraph in the Office action mailed 03 January 2008 is withdrawn in view of the explanations filed 03 July 2008.

Claim Rejections - 35 USC § 103

This rejection is maintained and reiterated from the previous office action, mailed 03 January 2008.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al.

The instant claims are drawn to a method for increasing the content of B-sheet secondary structure in recombinant amyloidogenic proteins by mixing negatively charged lipids with amyloidogenic proteins at a temperature and exposing the mixture to a conversion temperature for a time sufficient to increase the B-sheet secondary structure in the proteins.

Kleinschmidt et al. shows a method for increased B-sheet formation when Outer Membrane Protein A folds into a Beta Barrel as it inserts into a lipid bilayer, (DOPC is negatively charged at pH 8.5, see figure 1), at various temperatures, (see page 5011, right column, second paragraph, Figure 6).

Kleinschmidt et al. does not show the method utilizing an amyloidogenic protein.

Pan et al. shows the conversion of alpha-helices into beta-sheets of amyloid proteins.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of observing increased beta-sheet formation with the insertion of protein into a lipid bilayer of Kleinschmidt with use of amyloid proteins by Pan et al. because by Pan shows attempts of producing beta-sheet containing soluble amyloid protein, (see page 10965, second paragraph - page 10966, last paragraph).

Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al. and Barrow et al.

Kleinschmidt et al. is applied as above to claim 1.

Regarding claims 2 and 3, Martinez-Senac et al. teaches the increased beta-sheet formation of amyloid peptide when interacting with negatively charged phospholipids vesicles, (see page 746, left column, fifth paragraph; page 751, left column, second paragraph). Martinez-Senac et al. teaches the preparation of

amyloid peptide in association with negative charged phospholipids dissolved in water formed fibrils, (see page 747, left column, second paragraph).

Kleinschmidt et al. in view of Pan et al. in further view of Martinez-Senac et al. do not teach actively destroying the lamellar lipid structures.

Barrow et al. teaches that once a beta-sheet structure is formed in amyloids, the structure leads to the formation of insoluble amyloid fibrils, (page 253, middle column, first paragraph – right column, second paragraph). Barrow et al. teaches that in aqueous solutions, in the absence of TFE, at either low or high pH the amyloid peptides are 100% beta-sheet, causing an insoluble gel to form (page 253, middle column, first paragraph – right column, second paragraph).

One would be motivated to disperse the micelles surrounding amyloid protein with the advantage of showing the amyloid protein was increasing in beta-sheet secondary structure with the formation of insoluble fibrils that occur when amyloid protein is exposed to water. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Martinez-Senac et al. by putting the vesicles in an environment, such as pure water, that would destroy the micelles surrounding the amyloids to produce the insoluble amyloid fibrils as implied by Martinez-Senac et al. and taught by Barrow et al.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al. and Gursky et al.

Kleinschmidt et al. is applied as above to claim 1.

Regarding claims 4 and 5, Marinez-Senac et al. teaches the increase of beta-sheet formation in amyloids with negatively charged vesicles, (see above).

Kleinschmidt et al. in view of Pan et al. in further view of Marinez-Senac et al. do not teach the increase in beta-sheet formation with increase in temperature.

Gursky et al. provides a method for the temperature-dependent beta-sheet formation in amyloids in water. Gursky et al. teaches the increase of beta-sheet formation with the increase of temperature from 0 to 98°C at a rate of 15 deg/h, (see figure 2, page 98, right column, last paragraph – page 99, right column, first paragraph).

One would be motivated to increase the temperature of the solution of amyloid and vesicles with the benefit of increasing the interaction of the phospholipids and the amyloid peptide and thus increase in beta-sheet formation. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Marinez-Senac et al. by increasing the temperature once all components of the mixture were added as taught by Gursky et al.

Claims 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al. and Luhrs et al. (IDS) and Vold et al.

Kleinschmidt et al. is applied as above to claim 1.

Regarding claim 6, Marinez-Senac et al. teaches the increase of beta-sheet formation in Alzheimer beta-amyloid peptide, with negatively charged vesicles.

Kleinschmidt et al. in further view of Marinez-Senac et al. do not teach utilizing amyloidogenic proteins involved in Transmissible Spongiform Encephalopathy (TSE).

Luhrs et al. teaches the use of amyloid protein involved in Transmissible Spongiform Encephalopathy (TSE), (see introduction) in monitoring beta-sheet formation in negatively charged vesicles, (see figure 1, 3 and conclusion). Pan et al. teaches the conversion of alpha-helices into beta-sheets in the formation of the scrapie prion proteins. Pan et al. teaches that the conversion of alpha-helices in the prion protein into beta-sheets is likely to be the primary lesion in the illness of Spongiform Encephalopathy, page 10965, second paragraph). Pan et al. teaches similar proteins that undergo the conversion of alpha-helices into beta-sheets are betaA4 peptides involved in Alzheimer disease, (see page 10966, first paragraph).

One would be motivated to utilize other proteins that undergo beta-sheet formation that have the propensity to form insoluble fibrils with the benefit of

showing the method was applicable to other amyloid class proteins and their associated diseases. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Marinez-Senac et al. by utilizing a protein associated with Transmissible Spongiform Encephalopathy (TSE).

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al. and Vold et al.

Kleinschmidt et al. is applied as above to claim 1.

Regarding claims 7 and 8, Martinez-Senac et al. teaches the increased beta-sheet formation of amyloid peptide when interacting with negatively charged phospholipid vesicles, made from DMPC, DMPS, DMPG and other members of the phosphocholine family (see page 745, left column, third paragraph).

Kleinschmidt et al. in view of Pan et al. in further view of Martinez-Senac et al. do not teach the preparation of negatively charged vesicles with DMPX or DHPC.

Vold et al. teaches magnetically oriented phospholipid bilayered micelles for structural studies of polypeptides. Vold et al. teaches the binary mixture of long and short chain phosphatidylcholines such as DMPC and DHPC to be consistent with disk-shaped phospholipid aggregates, (see page 267, left column, first paragraph).

One would be motivated to utilize other phosphocholine family members that allowed for the production of charged phospholipid bilayered micelles for the benefit of exploiting lipids that may be more appropriate for particular biological systems. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Marinez-Senac et al. by utilizing other phosphocholine family members such as DMPX or DHPC.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kleinschmidt et al. in view of Pan et al. as applied above in claim 1, and in further view of Martinez-Senac et al.

Kleinschmidt et al. is applied as above to claim 1.

Kleinschmidt et al. in view of Pan et al. do not teach a conversion buffer with the pH below the isoelectric point of the recombinant amyloidogenic proteins.

Regarding claim 9, Martinez-Senac et al. teaches buffer pH at 3.0, (see figures 3 and 4). This pH is below the beta amyloid peptide isoelectric point of 5.0, (see page 13919, second column, second paragraph).

One would be motivated to use buffers with pH below the isoelectric point of amyloid proteins with the benefit of increase in beta-sheet formation without aggregation. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Kleinschmidt et al. in view of Pan et al. by using low pH conversion buffer as taught by Martinez-Senac et al.

Response to Arguments

Applicant's arguments filed 03 July 2008 have been fully considered but they are not persuasive.

Applicants' argue that Kleinschmidt et al. provides very specific protein forced to unfold and fold in harsh conditions. Kleinschmidt et al.'s protein is prokaryotic and not related to mammalian amyloid proteins. Likewise, Kleinschmidt et al. method is not directly related to beta sheets but to beta hairpins and there is no increase in beta sheet formation. Applicants' argue that Pan et al. shows a discussion of converting alpha helix/beta sheet conversion and subsequent precipitation and the basis for the Examiner's rejection is missing. Applicants' argue that because of the sequence and structure difference between Kleinschmidt et al.'s protein and amyloid proteins that no one skilled in the art would look to Kleinschmidt et al. to provide useful teaching of an increase in beta sheet formation. Applicants' argue that lamellar structures differ from normal micelle structures and are critical in the beta sheet formation and the cited art does not use or suggest lamellar structures.

Applicants' arguments are not persuasive.

Proteins are typically made from 20 naturally occurring amino acids. Some amino acids are hydrophobic, some hydrophilic and some are considered neutral. A protein structure that has a globular hydrophobic core, alpha helical or beta sheet formation result from concentrations or clusters of the categories of the naturally occurring amino acids mentioned above. Likewise, these clusters or concentrations of amino acids and their subsequent structures are universal, i.e.

prokaryotic, mammalian, both have proteins that are globular, alpha helical and beta sheet forms. Simply put, a protein with a concentration of certain types of amino acids will tend to form particular structures in a certain environments, despite the origin of the protein sequence. This was the point of Pan et al., (page 10962, right column). It is common in the art to utilize urea, sodium dodecyl sulfate and a hundred other similar chemicals as agents to catalyze the formation of secondary structures despite the origin of the protein. If such a method is successful on similar structured proteins as the invention, i.e. beta sheet structures, then one skilled in the art would certainly consider those teachings. Kleinschmidt et al. shows a globular structure increasing in beta sheet formation to form a beta barrel, (beta sheet), (page 5007, left column; Figure 11). Lamellar structures and micelle structures have the same important structure, a lipid bilayer that provides a hydrophobic environment. That is the critical environment for beta sheet formation and that is what Kleinschmidt et al. shows, (Figure 11).

All the elements of the claims are provided within the cited art. KSR International Co. v. Teleflex Inc., provides a rationale wherein a claim would have been obvious because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product, not of innovation but of ordinary skill and common sense. Motivation is not required to make a prima facie case of obviousness. It is enough to have a likelihood of success with known technical features in the prior art. Kleinschmidt et al. shows an increase in beta sheet formation in lamellar environment. Pan et al. show amyloid protein may change

secondary structure under certain conditions. It would be obvious to try to increase beta sheet formation of amyloid proteins with the method of Kleinschmidt et al.

Applicants' argue the remaining cited art does not remedy the deficiencies set forth by Kleinschmidt et al. and Pan et al. This argument is not convincing because Kleinschmidt et al. and Pan et al. teach all limitations of the instant invention and have no deficiencies.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LARRY D. RIGGS II whose telephone

number is (571)270-3062. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shubo (Joe) Zhou/
Primary Examiner, Art Unit 1631

/LDR/
Larry D. Riggs II
Examiner, Art Unit 1631